REMARKS/ARGUMENTS

Upon entry of the above claim amendments, Claims 1-15, 17, and 19-24 are pending in the present application.

Claims 1-3 are instantly amended to more clearly define the subject matter that Applicants deem to be their invention. Specifically, the definition of R7 in Claims 1-3 has been amended to requires that "C_1-C_6-alkyl" is substituted by various groups recited therein rather than having substitution optional (as recited in claims as originally filed). Support for the amendments can be found in the claims as originally filed and also throughout Applicants' specification, especially in numerous compounds listed in the Examples.

Claims 15 and 17 are instantly amended to more clearly define the subject matter that Applicants deem to be their invention. Support for these amendments can be found in the claims as originally filed.

Claim 19 is instantly amended to correct certain typographical errors.

Claims 22 and 23 are new and are directed to compositions comprising a compound of Formula (IA). Support for these claims can be found in Claims 15 and 17 as originally filed.

Claim 24 is new and is directed to compounds that are covered in claims originally filed, and specifically disclosed in Example 17 of Applicants' specification.

No new matter has been added in the above claim amendments.

Applicants respectfully reserve the right to pursue any non-elected, canceled or otherwise unclaimed subject matter in one or more continuation, continuation-in-part, or divisional applications.

Reconsideration and withdrawal of the objections to and the rejections of this application in view of the amendments and remarks herewith, are respectfully requested, as the application is in condition for allowance.

Rejections under 35 U.S.C. § 112, First Paragraph

Claims 19-21 have been rejected under 35 U.S.C. 112, First Paragraph, as allegedly failing to provide enablement with respect to methods of treating acute and chronic inflammatory, ischaemic or remodeling processes. While noting that the instant compounds

demonstrate HNE inhibiting activity, the Examiners alleges that "there is no nexus in the specification how this activity relates to all types of diseases of the claims" (see pages 5 and 6 of the Office Action). Furthermore, the Examiner alleges that "Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds." Applicants respectfully disagree with the Examiner's allegations.

With regard to the methods of treatment of the present claims, the test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *U.S. v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988). The examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *Manual of Patent Examining Procedure* ("MPEP") § 2164.04 (citing *In re Wright,* 999 F.2d 1557, 1562 (Fed. Cir. 1993)).

Accordingly:

> A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must be taken as being in compliance with the enablement requirement* ... unless there is a *reason to doubt the objective truth of the statements* contained therein which must be relied on for enabling support
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> It is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.

Id. (emphases added).

Applicants respectfully submit that whether or not the scope of a claim is broad is irrelevant to the assessment of the enablement of the claim. The question is whether those skilled in the art would have been able to make and use the claimed invention based on the disclosure. *(See U.S. v. Telectronics, Inc.,* at 785).

Applicants respectfully submit that Claims 19-21 are enabled because the specification "contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented." *Id.*

Here, enabling disclosure has been made in the present application to treat acute and chronic inflammatory, ischaemic or remodeling processes. For example, it is within common knowledge of the art that "HNE is released from activated PMN and has been implicated causally in the pathogenesis of acute and chronic inflammatory diseases" (*see* lines 14-15 at page 1 of Applicants' specification published as WO 2004/024700). It follows naturally that people skilled in the art can predict, without undue experimentation, that HNE inhibitors (such as, compounds in the present application) are suitable for the preparation of medicaments for treating acute and chronic inflammatory diseases. This is consistent with previous research results in field, which have demonstrated that HNE inhibitors are useful in treating inflammatory diseases (*see* R.A. Stockley, *Neutrophils and protease/antiprotease imbalance,* Am. J. Respir. Crit. Care, 160, S49-S52 (1999), the disclosure of which has been incorporated at page 2 in the present application).

Furthermore, it is disclosed in the present specification that the claimed compounds can be prepared by synthetic procedures described in the Examples.

In addition, the instant specification discloses various assays which can be readily performed by one of ordinary skill in the art. For example, *in vitro* HNE inhibition assays are disclosed at pages 24-26, and *in vitro* human neutrophil assays are discussed through pages 26 to 28. In view of the whole disclosure and common knowledge in the art, Applicants submit that there is an enabling disclosure in Applicants' specification with respect to methods of treating acute and chronic inflammatory diseases by using compounds instantly claimed.

Similarly, Applicants' specification provides enabling disclosure on methods for treating ischaemic or remodeling processes (*see* lines 28-31 at page 1, lines 7-18 at page 2, and lines 14-

20 at page 21 of the present application). Also, *in vivo* rat models on testing instant compounds on ischaemic or remodeling processes are discussed in great length at pages 28-30 of the present application. Accordingly, the enablement requirement for methods for treating ischaemic or remodeling processes has been satisfied in Applicants' specification.

In view of the foregoing, it is clear that sufficient guidance is provided in the specification so as to allow those of ordinary skill in the art to use methods of treatment on diseases claimed herein. Indeed, the claimed invention is directed to the use of obtainable compounds. People skilled in the art can readily determine the activity for any of the compounds encompassed by the claims by using the assays described in the specification, which can be readily used to determine that a compound in the present invention is useful in the treatment of the diseases recited in the claims. Moreover, the determination by a physician as to whether a claimed compound is effective in treating a recited disease in a given patient is a type of determination that is always made by physicians for every pharmaceutical. Indeed, the determination is a routine one that every physician is prepared to make, and which requires little or no effort. Therefore, Applicants respectfully submit that one reasonably skilled in the art could make or use the invention as claimed without undue experimentation.

At least for the above-stated reasons, Applicants respectfully request reconsideration and withdrawal of the rejections of Claims 19 to 21 under 35 U.S.C. § 112, First Paragraph.

Rejections under 35 U.S.C. § 102(b)

Claims 1-3, 6, 9-11, 15 and 17 have been rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Lewandowski *et al.* (J. Comb. Chem. 1999, 1(1), 105-112; hereinafter "Lewandowski"). In particular, the Examiner alleges that these claims have been anticipated by Compound 27 in Table 1 at page 108 of Lewandowski. Applicants respectfully disagree.

Nevertheless, without conceding the validity of the Examiner's allegation and solely for facilitating the prosecution of the present application, the afore-mentioned claims have been amended as that compounds of Formula (I) cannot have both of R^3 and R^7 as methyl groups (as recited in Lewandowski). Therefore, the compounds recited in the afore-mentioned claims are novel in view of Lewandowski. Accordingly, reconsideration and withdrawal of the rejections on Claims 1-3, 6, 9-11, 15 and 17 under 35 U.S.C. 102(b) are respectfully requested.

Rejections under 35 U.S.C. § 103(a)

Claims 1-6, 8-11, 15, 17 and 19-21 have been rejected under 35 U.S.C. 103(a) as allegedly being obvious over Namazi *et al.* (J. Het. Chem. 2001; hereinafter "Namazi"). In particular, the Examiner alleges that compounds 1-11 disclosed at pages 1051-1052 of Namazi differ from the presently claimed compounds only by a methyl group (*see* page 8 of the Office Action). Furthermore, the Examiner alleges that the Namazi compounds and the presently claimed compounds are expected to possess similar properties and that one skilled in the art will be motivated to modify the Namazi compounds to reach the presently claimed compounds (*see* pages 8 and 9 of the *Office Action*). Applicants respectfully note that the Examiner has not provided any of the references alluded to by this statement.

To properly determine a prima facie case of obviousness, the Examiner "must step backward in time and into the shoes worn by the hypothetical 'person of ordinary skill in the art' when the invention was unknown and just before it was made." M.P.E.P § 2142. This is important as "impermissible hindsight must be avoided and the legal conclusion must be gleaned from the prior art." *Id.* Three criteria may be helpful in determining whether claimed subject mater is obvious under 103(a): first, if there is some suggestion or motivation to modify or combine the cited references; second, if there is a reasonable expectation of success; and third, if the prior art references teach or suggest all the claim limitations. *KSR Int'l Co. v. Teleflex, Inc.* No 04-1350 (U.S. Apr. 30, 2007). With regard to the first criterion, the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.3d 690 (Fed. Cir. 1990). "Knowledge in the prior art of every element of a patent claim ... is not of itself sufficient to render claim obvious." *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966); *Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1333-34 (Fed. Cir. 2002)]. The issue is whether there is an apparent reason to combine the known elements in the fashion claimed by the patent at issue. *KSR Int'l Co. v. Teleflex, Inc.*

Here, the Examiner has alleged that a skilled artisan would be motivated to modify the Namazi compounds to reach the presently claimed compounds. Nevertheless, the Examiner fails

to give any support for such allegation. As a matter of fact, Namazi only discloses how to make the specific compounds disclosed therein and the chemical properties associated with compounds synthesized. Indeed, Namazi does not disclose any biological test data associated with those compounds. Accordingly, Applicants respectfully submit that there is no such suggestion or motivation in Namazi to modify the compounds disclosed therein as alleged by the Examiner.

Further, the Examiner has asserted that a modification from hydrogen on phenyl to methyl on phenyl (now as tolyl group) would not alter or affect properties of these compounds. This is an unjustified assertion. As a matter of fact, it is well known in the art that phenyl group (as in the Namazi compounds) behaves differently than tolyl group (as in the claimed compounds). For example, it is found that a methyl group makes benzene around 25 times more reactive than benzene itself in reactions of electrophilic aromatic substitution (*see*, for example, B. S. Furnell et al., *Vogel's Textbook of Practical Organic Chemistry*, 5th edition, Longman/Wiley, New York, 1989; L. G. Wade, *Organic Chemistry*, 5th ed., p. 871, Prentice Hall, Upper Saddle River, New Jersey, 2003; and also J. March, *Advanced Organic Chemistry*, 4th ed., p. 723, Wiley, New York, 1992). As such, a skilled artisan would not reasonably expect that same properties will be obtained once a phenyl compound (in Namazi) is modified to a toyl compound.

Nevertheless, without conceding the validity of the Examiner's allegations and solely for purpose of expediting the allowance of the present application, Applicants have amended the claims to require that the C_1-C_6-alkyl group as R^7 is "substituted with one to three identical or different radicals selected from the group consisting of halogen, hydroxy and C_1-C_4-alkoxy." Applicants respectfully submit that: first, the instantly claimed compounds are completely different in structures from the Namazi compounds; second, there is no teaching or motivation in Namazi to modify compounds disclosed therein; third, there is no justifiable expection for success to modify Namazi compounds to reach the instantly claimed compounds, since a skilled artisan would conclude that the compounds as claimed behave completely differently from the

Namazi compounds. Therefore, the compounds now claimed are patentably distinct over the Namazi disclosure.

At least for the foregoing reasons, the present invention is patentably distinct over Namazi. Accordingly, reconsideration and withdrawal of the rejections on Claims 1-6, 8-11, 15, 17 and 19-21 under 35 U.S.C. 103(a) are respectfully requested.

Double-Patenting Rejections

Claims 1-15, 17 and 19-21 have been provisionally rejected on the grounds of nonstatutory obviousness-type double patenting over pending claims of each of co-pending of U.S. Patent Application No. 10/590,786 or 10/590,770.

As it remains unknown what subject matter claimed and disclosed in the present application (also that disclosed in the co-pending applications) will be deemed allowable, any statement regarding these rejections made on Applicants' part is premature. Accordingly, Applicants respectfully traverse these rejections, and request that these rejections either be withdrawn as stated above, or be held in abeyance until subject matter is deemed allowable in this application.

CONCLUSION

In view of the remarks made herein, the application is believed to be in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are respectfully requested. Please charge any required fee or credit any overpayment to Deposit Account No. 04-1105, Order No. 82439 (303989).

Dated: November 24, 2008

Respectfully submitted,

By: _____

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